

## Mapping preserved real-world cognition in severely brain-injured patients

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### 1. ABSTRACT

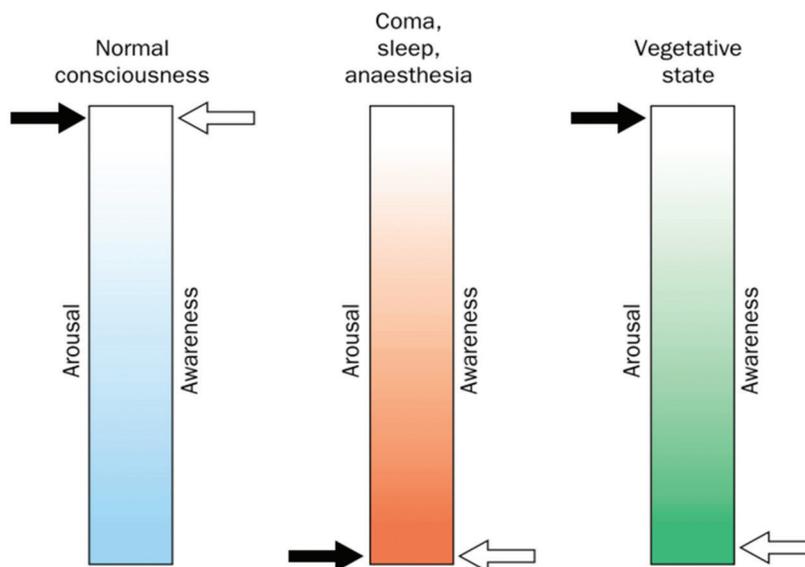
Decoding the contents of consciousness from brain activity is one of most challenging frontiers of cognitive neuroscience. The ability to interpret mental content without recourse to behavior is most relevant for understanding patients who may be demonstrably conscious, but entirely unable to speak or move willfully in any way, precluding any systematic investigation of their conscious experience. Until recently, patient studies have used structured instructions to elicit willful modulation of brain activity according to command. Recent work has used a different approach, where the similarity of any given patient's brain activity to that of healthy controls during naturalistic paradigms can help detect high-level cognition and consciousness. This approach is easy to administer, brief, and does not require compliance with arbitrary task instructions. Therefore, it is suited to probing consciousness and revealing residual cognition in highly impaired comatose patients, thus helping to improve diagnosis and prognostication for this vulnerable patient group.

### 2. INTRODUCTION

Disorders of consciousness, arising from a variety of etiologies, can render a person incapable of overt behavioral responses, and these patients may also be unaware of themselves and the outside world (1). An accurate diagnosis and understanding of a patient's current state are critical for not only the patient's medical care and quality of life, but also have wide-ranging implications for their family and the medical teams that care for them.

Following severe acute brain injury, neurological disorders that cause impairments to a patient's awareness of the self and surroundings are termed disorders of consciousness (DoC). Coma, the vegetative state (VS), and the minimally conscious state (MCS) are all considered disorders of consciousness (2) (Figure 1). After injury, patients can progress through various disorders of consciousness states before recovering consciousness, or may maintain a disorder of consciousness diagnosis permanently.

Two dimensions are important when discussing disorders of consciousness, each of them existing on a continuum (3). The first is arousal (also known as wakefulness), which refers to a person's sleep-wake cycles and the ability to open one's eyes. A person is considered to have wakefulness if they can open their eyes and possess sleep-wake cycles. The second dimension, awareness, refers to one's awareness of the self and surroundings. It also concerns conscious perception, cognition and memories of past experiences. Awareness, also known as consciousness, exists on a continuum, meaning it is not an all-or-nothing concept (4). The term 'disorders of consciousness' is used to describe a state in which there is a disruption in the normal relationship between awareness and arousal, such that one can exist without the other. Individuals can exist at different levels on each dimension, and certain combinations of wakefulness and awareness are characteristic of different conditions and clinical diagnoses.



**Figure 1.** Awareness and arousal levels for disorders of consciousness. The level of awareness (of oneself and surroundings) and arousal (eye opening, sleep-wake cycles) for different states of intact, altered or absent consciousness are depicted. (Reproduced and adapted with permission from Laureys, Owen & Schiff, 2004).

## 2.1. Coma

After traumatic (i.e. motor vehicle accident or blunt trauma) or non-traumatic (i.e. hypoxia from cardiac arrest or stroke) acute brain injury, patients may initially be diagnosed as being in a coma. A coma is defined as having low arousal (eyes are closed) and low awareness (3). From the comatose state, patients may transition to a variety of outcomes, including recovery. However, some patients do not regain full awareness and are later diagnosed as being in a vegetative state, minimally conscious state, or having a locked-in syndrome.

## 2.2. Vegetative state

The progression from coma to vegetative state occurs when a patient opens their eyes, indicating they have regained arousal, yet this is not accompanied by regained awareness. VS patients have wakefulness, but are unaware of themselves and their surroundings, are unable to respond to external stimuli and are unable to communicate. However, they are able to breathe on their own without the aid of a mechanical ventilator (4). The term “permanent vegetative state” is assigned to individuals who have maintained this condition for one year in the case of traumatic injury, or six months for non-traumatic injury (2).

## 2.3. Minimally conscious state

Compared to the vegetative state, the minimally conscious state is characterized by higher levels of awareness, meaning limited and inconsistent but reproducible signs of consciousness (though levels of awareness have not yet reached that of a healthy individual). MCS patients may show reproducible

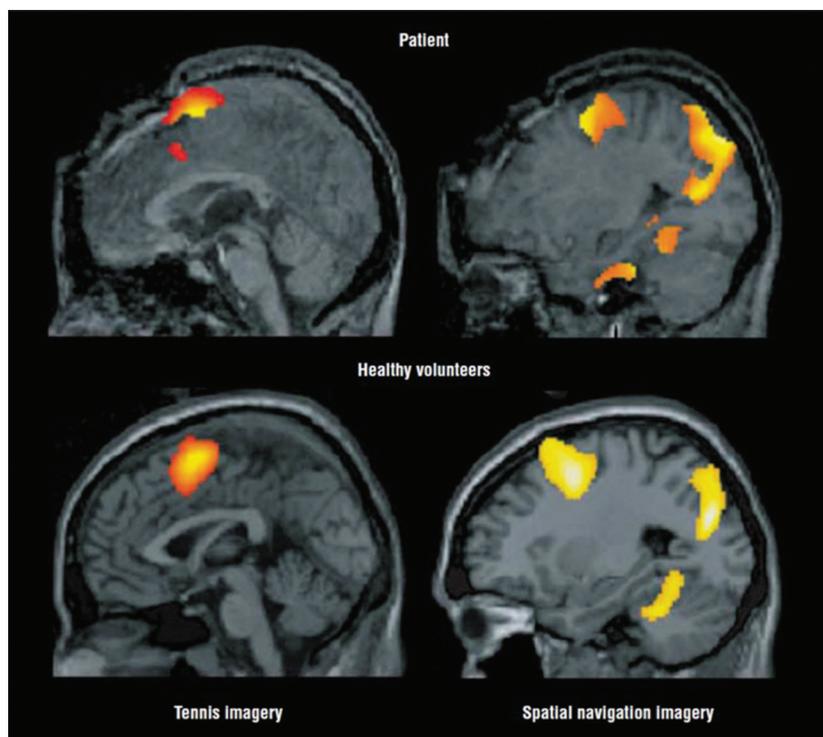
command-following, non-reflexive purposeful movement, and/or verbal or gestural yes/no responses (2). Emergence from the minimally conscious state occurs when a patient can functionally communicate or perform functional use of objects (5).

## 2.4. Locked in syndrome

Patients who are totally paralyzed, but still maintain the ability to use vertical eye movements or blinking to communicate, are diagnosed with locked-in syndrome (LIS) (6). LIS is not considered a disorder of consciousness because patients are known to be fully conscious. This condition is generally caused by brainstem lesions, but can also be the result of traumatic brain injury. These patients are difficult to diagnose due to the similarity between LIS and VS/MCS, and LIS patients may have fluctuating levels of arousal in the acute state of their condition, leading to signs of consciousness to be missed during assessment. Most patients diagnosed with LIS as a result of an acute brainstem lesion maintain normal cognitive abilities and full awareness, but cannot perform most motor movements.

## 2.5. Diagnosing disorders of consciousness

Standardized behavioral scales are used to objectively evaluate awareness at the bedside. A behavioral scale commonly used for DoC patients is the JFK Coma Recovery Scale- Revised (JFK CRS-R) (7). This scale is composed of six subscales evaluating auditory, visual, motor and verbal functions, as well as communication and arousal (eye opening) (8). The CRS-R can provide a diagnosis of vegetative state, minimally conscious state or emergence from minimally



**Figure 2.** Command-following via mental imagery in one patient clinically diagnosed as being in a vegetative state. The top panel shows the brain activation in responses of the supplementary motor area (SMA) during tennis imagery, and the parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) during imagery of spatial navigation, in a patient who fulfilled all of the internationally agreed criteria for the vegetative state. These responses were indistinguishable from that of a group of healthy volunteers, shown in the bottom panel. (Reproduced and adapted with permission from Owen *et al.*, 2006).

conscious state, depending on the score obtained at the bedside.

However, the inability of a patient to overtly communicate and follow behavioral commands, as measured by the CRS-R, does not always imply absence of consciousness. Since the CRS-R behavioral scale relies on overt behavior and motor movement, it may not detect awareness in some DoC patients if they have motor impairments (9). Up to 43% of patients have been shown to be misdiagnosed as VS when they do in fact show signs of awareness (8). That is, some patients are diagnosed as VS after routine bedside assessment, but after more thorough bedside testing, inconsistent but reproducible behavioral signs of awareness are observed. These inconsistent signs of awareness would reclassify a patient as MCS after an initial misdiagnosis of VS.

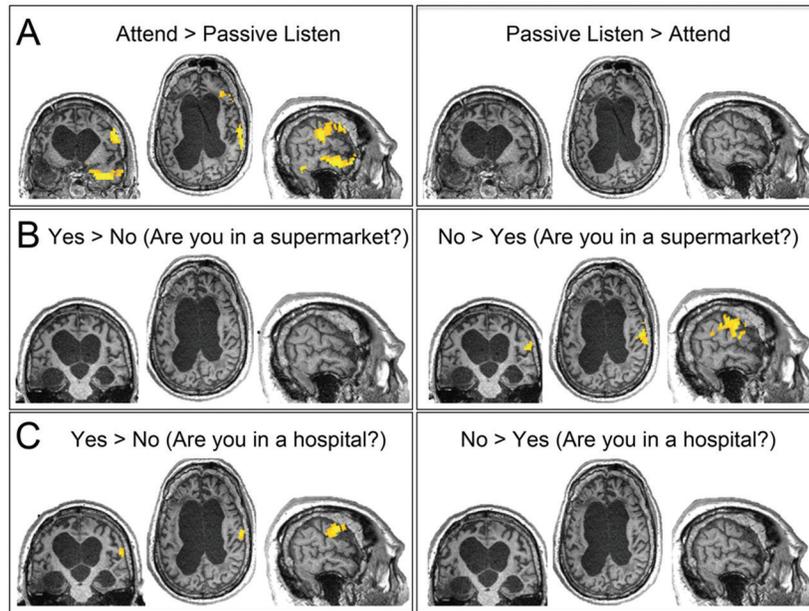
### 3. COMMAND-FOLLOWING PARADIGMS FOR DETECTING COVERT AWARENESS

Neuroimaging can provide a more sensitive measure of consciousness in DoC patients (10-12). In these tests, brain activity is used as a proxy for behavior (13). The results from neuroimaging tests can

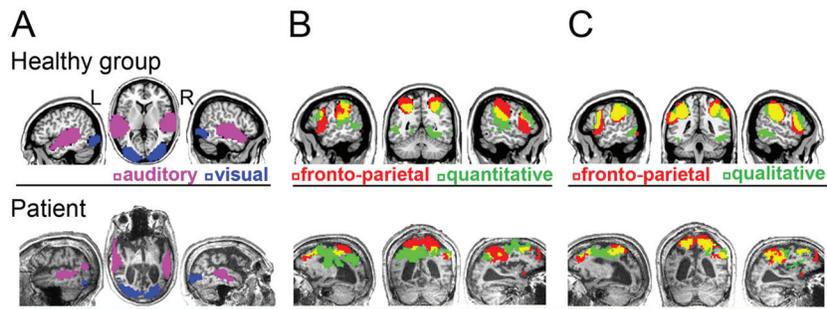
challenge the initial diagnosis given to a patient and may aid in further understanding their abilities and disabilities.

One category of tasks used for testing covert awareness in DoC patients is termed command-following. A command-following task requires a patient to actively comply with the task instructions and follow structured commands provided to them (14). In an example of a command-following task, Owen *et al.* tested if DoC patients could perform mental imagery in the fMRI scanner (Figure 2-4) (15). They designed a task that involved healthy controls and DoC patients performing mental imagery, such as imagining playing tennis or navigating around the rooms in a house. The mental imagery tasks (“tennis” and “house”) produced distinct activation patterns in controls. Further, a VS patient produced the same activation patterns when imagining the same scenarios. The patient’s ability to follow mental imagery instructions during these tasks provided strong evidence that she was conscious.

Monti *et al.* extended the mental imagery paradigm to communicate with a non-responsive patient (13). The patient used mental imagery to accurately answer binary questions in the scanner, by imagining “tennis” to answer “yes” and “house” to



**Figure 3.** Command-following and communication via selective attention in a patient clinically diagnosed as being in a vegetative state. Brain activity is overlaid on the patient’s native anatomic volume. The opposite directions of each contrast (i.e. *Attend > Passive Listen* or *Passive Listen > Attend*) are shown on the left and right sides of each panel. A) The command-following scan also served to localize the brain foci of attention unique to the patient. B and C) Selective attention to the answer word (either yes or no) during each communication scan was investigated within these regions. Attention to the answer in each question (B, no; C, yes) significantly activated the precentral or motor region. (Reproduced and adapted with permission from Naci and Owen 2013).



**Figure 4.** Decoding executive function in one patient thought to lack consciousness. Healthy group: (A) Group-level auditory (purple) and visual (blue) ICs. (B–C) The healthy group’s activity predicted by the quantitative (B)/qualitative (C) executive measure (green) is overlaid on the group fronto-parietal IC (red); overlap areas are displayed in yellow. Patient: (A) The healthy group’s auditory and visual ICs predicted significant activity in the Patient’s auditory (purple) and visual (blue) cortex, respectively. (B–C) The quantitative (B) and qualitative (C) executive measures predicted activity (green) in the Patient’s frontal and parietal regions. Overlap with activity predicted by the healthy group’s fronto-parietal IC (red) is displayed in yellow. (Reproduced and adapted with permission from Naci *et al.*, 2014).

answer “no”. This patient was believed to lack awareness following bedside assessment, but neuroimaging results from this command-following task indicated that he was indeed aware and could communicate by modulating his brain activity.

In another example of a command-following task, researchers used fMRI to measure brain activity during a selective auditory attention task to determine if this could serve as a communication tool for DoC patients (12, 16). The task introduced by Naci *et al.* had independent

command-following and communication sessions (16). During the command-following session, participants followed instructions to either selectively attend to the presentation of a target word while ignoring a non-target word (either “yes” or “no”), or relax. In the communication sessions, they used this method for brain-based binary communication, by willfully choosing the target word to attend to, either “yes” or “no”, depending on the answer to the specific question, and then relaxing when the non-answer word was presented. Healthy controls showed significant activation in the attention network during

the 'attend' significantly more than the 'relax' trials, and successfully used selective attention to answer binary questions, by selectively attending to the word that corresponded to the correct answer. Additionally, Naci and Owen showed that two out of the three DoC patients tested, one clinically diagnosed as VS and the other as MCS, used selective attention during the fMRI scanning to correctly answer several questions (12). This study established another command-following task that could be used to test covert awareness and to communicate with DoC patients, and therefore strengthened the argument that some behaviorally non-responsive patients who fulfill the internationally agreed upon criteria of the Vegetative State retain covert awareness.

However, cohort studies show that only 17-19% of vegetative patients respond to command-following tasks (10, 13). Beyond a genuine lack of awareness in the remaining 80% of the patients, the lack of responses may be due to a variety of reasons, including the patient's inability to understand the task, unwillingness to comply with the task, fluctuating levels of consciousness, or their inability to act on the commands, even if they are understood (17). It is well established that brain damaged patients have difficulty sustaining attention for long periods of time (18), and command-following tasks require sustained attention over several minutes in order to comply with structured instructions.

### 4. NATURALISTIC PARADIGMS FOR DETECTING COVERT AWARENESS

To address this challenge, Naci *et al.* (19-21) established a novel neuroimaging paradigm for testing for covert awareness in behaviorally non-responsive patients who are covertly aware but unable to follow commands. This type of paradigm fits into a category termed 'naturalistic', because it presents ecologically valid, dynamic and complex stimuli in the absence of task instructions. In contrast to command-following paradigms, it investigates active cognitive processes, such as executive function, that are naturally recruited during the presentation of richly evocative stimuli, akin to real-world events, without any external experimental constraints. By mimicking real-world experiences this paradigm engages attention naturally and, thus, is less strenuous for brain-injured patients (14). Moreover, it puts patients at ease, helping them to remain still in the scanner and ensuring more accurate assessment of brain activity.

The underlying rationale in these studies was that in everyday life, different individuals engage in a number of shared activities, such as going to the movies, and therefore have similar conscious experiences. Naci and colleagues asked whether a similar neural code underlies these similar conscious experience in different individuals that could be used to interpret conscious

experiences in patients who cannot produce willful behavior or self-report.

For example, engaging movies, in particular, are designed to give viewers a shared conscious experience driven, in part, by the recruitment of similar executive processes, as each viewer continuously integrates their observations, analyses and predictions, while filtering out any distractions, leading to an ongoing involvement in the movie's plot. These cognitive integrative processes enable viewers to understand a movie.

Naci *et al.* used a suspenseful movie by Alfred Hitchcock – 'The Master of Suspense' – to evaluate the conscious experience of viewers, as they freely watched a brief (five minute) edited clip inside the functional Magnetic Resonance Imaging (fMRI) scanner (19). Similarly to previous studies (22) they found highly synchronized activity across the healthy participants throughout the brain. However, prior to Naci *et al.* it was not known whether any of these synchronized activity fluctuations reflect similar executive function across different individuals in response to the evolving executive demands of the movie plot (19).

They focused in particular in the synchronized brain activity in frontal and parietal regions, known to support executive function (23-26). Not only did these regions display high synchronization across participants, but also this synchronization was absent when participants were presented with a scrambled version of the movie, which lacked a coherent plot.

Moreover, researchers found that the movie's executive demands, assessed quantitatively with a dual-task procedure in an independent group, predicted activity in these frontal and parietal regions. Importantly, the ratings of suspense obtained in yet another independent group of participants throughout the movie showed significant inter-subject correlation, this confirming the common conscious experience of individuals watching it. Similarly to the executive demands, the ratings of suspense predicted activity in the frontal and parietal regions. Together, these results suggested that the movie's executive demands drove brain activity in frontal and parietal regions, and, further, that the synchronization of this activity across individuals underpinned their similar experience. More broadly, these findings suggested that there is a common neural code that underpins similar conscious experiences, which could be used to decode these experiences in the absence of behavior.

In support of this idea, the same approach generated strong evidence for intact consciousness in an entirely behaviorally non-responsive brain-injured patient. The patient, who had remained behaviorally non-responsive for a 16-year period prior to the fMRI scanning, demonstrated a highly similar brain response

to that of the three independent groups of healthy participants. The patient's brain activity in frontal and parietal regions was tightly synchronized with the healthy participants' over time, and crucially, it reflected the executive demands of specific events in the movie, as measured both qualitatively and quantitatively in healthy individuals. These neuroimaging results were striking in light of the patient's behavioral profile observed in repeated assessments at his bedside, over the 16-year period. During that time, the patient showed neither movement to command, nor any behavioral signs of functional or non-functional communication. He displayed no signs of localization of sound, and no visual recognition or interaction with objects or people in his environment, including his family members. By contrast, the patient's brain response to the movie suggested that he had a conscious cognitive experience highly similar to that of each and every healthy participant, while watching the same movie. These processes are likely to include updating the contents of working memory (e.g., to follow the plot), relating events in the movie to past experiences (e.g., to appreciate that a gun is a dangerous weapon), and coding the foreshadowing cues (i.e., events that might have future relevance to the plot) characteristic of movies of this type. Thus, the patient's brain response suggested that he could maintain much more complex mental processes than could ever be inferred based on his behavior, and retained a sophisticated cognitive repertoire. This included complex mental faculties not previously reported in these patients, such as theory of mind, the ability to make morally significant distinctions, and the capacity to experience emotions and reflect about one's own future states (21).

In summary, these studies (19, 21) demonstrated that fMRI-based naturalistic paradigms, which present highly engaging audio-visual movies, are suited for testing covert awareness in DoC patients. However, a proportion of vegetative state patients do not exhibit visual fixation, and this is a major impediment to processing visual information. Additionally, comatose patients in the acute stages post injury by definition have their eyes closed. For these reasons, audio-visual movies may not be effective stimuli to testing covert awareness in a substantial number of behaviorally non-responsive patients whose consciousness is at question. To address this shortcoming of audio-visual stimuli, Naci *et al.* developed a naturalistic paradigm that instead used auditory-only stimuli for testing covert awareness and executive function in DoC patients (20).

In this study, researchers presented healthy participants with rich auditory stimuli portraying real-world events in the form of short stories, as they lied inside the fMRI scanner. The short stories presented engaging and suspenseful narratives, as well as background music. One narrative, an opening episode from the movie "Taken", captured the attention of listeners and produced

significant inter-subject synchronization throughout the brain significantly more than the other stimuli. Using tensor independent component analysis (ICA) (27), the whole brain correlation was segmented into spatially distinct networks, including visual, auditory, motor, medial and frontoparietal networks. These networks were identified in each subject (single subject ICA) (28), and the two networks critical to understanding the story narrative—the auditory and the frontoparietal—displayed a highly robust inter-subject correlation (20). Moreover, the frontoparietal synchronization was not present when participants listened to a baseline stimulus that was unintelligible, suggesting the synchronization in this network was driven by a common understanding of the plot, and not merely due to exposure to an identical stimulus. This stimulus enabled reliable prediction of brain activity at the single subject level. During the narrative, 15/15 participants demonstrated significantly similar auditory, and 14/15 similar frontoparietal brain activity to the rest of the group.

Again, the inter-subject synchronization in the frontoparietal network during stimulus presentation is noteworthy because this network is involved in executive function, which is critical to our conscious experience of the world. Moreover, an independent study (29) found that the frontoparietal activity in response to this audio narrative was extinguished in deeply anesthetized unconscious individuals, further suggesting that the brain responses in these regions could not be realized without the presence of covert conscious awareness. Therefore, if a patient displayed similar activity in the frontoparietal network to the healthy group during the audio narrative, this would suggest the presence of executive function and covert awareness. Future application of this approach in comatose patients in particular will have important implications. The extreme prognostic uncertainty during coma, frequently biases medical decisions towards withdrawing life supporting therapies very early, within the first 72 hours (30). However, previous research in vegetative state patients suggests that, the lack of behavioral responsiveness in some cases does not preclude the presence of covert conscious awareness (10-13; 15, 19, 21, 31-33). Similarly, a proportion of comatose patients may be covertly aware, and may be able to demonstrate their consciousness by engaging in high-order cognitive processes, such as executive function, that can be detected via fMRI scanning. Pilot studies in comatose patients have revealed residual cognitive function, but no patient to date has demonstrated covert awareness through command following paradigms. This suggests that comatose patients may not have sufficient cognitive resources to modulate their brain activity in accordance with study instructions. By contrast, naturalistic viewing or listening is effortless and likely to be more effective for identifying the subset of acute comatose brain-injured patients, who remain aware, yet have not recovered

sufficient cognitive resources to modulate their brain activity according to commands. Moreover, follow-up scanning of comatose patients longitudinally from the acute phase through to the evolution of their condition to a stable clinical diagnosis, subsequent comparison between the residual cognitive profile of those patients who improve with those who deteriorate will help identify neural indicators of recovery early in the disease progression. This work could have profound medical and legal implications for the diagnosis, prognosis and end-of-life decisions for vulnerable comatose patients.

### 5. SUMMARY

Decoding the contents of consciousness in behaviorally non-responsive patients poses unique challenges. Until recently, patient studies have used structured instructions to elicit willful modulation of brain activity according to command, in order to decode the presence of willful brain-based responses in this patient group. These studies have shown that despite the apparent absence of external signs of consciousness, a significant minority patients with disorders of consciousness can respond to commands by willfully modulating their brain activity (10-13, 15, 31), and even respond to 'yes'/'no' questions, by performing mental tasks (11-13).

However, a proportion of behaviorally non-responsive patients may remain aware but unable to modulate their brain activity according to task commands. Naturalistic paradigms are highly suited for testing covert awareness in this category of patients (19-21). This recent approach has advanced our knowledge beyond previous work in important ways. First, it has provided a method to reduce the high rates (~43%) of patient misdiagnosis (8, 34, 35). Although previous neuroimaging methods have provided an important step in this direction, patient cohort studies show that 4 out of 5 patients do not respond to these neuroimaging tests (13). As they require compliance with arbitrary task instructions they are very effortful for some patients who, due to the effects of brain injury, fail to sustain attention to the structure of the task (18). Secondly, by contrast, the naturalistic approach is unconstrained by task commands, but rather, captures attention naturally, and therefore, might be more effective for detecting conscious awareness in this subset of patients. Moreover, naturalistic paradigms put patients at ease, helping them to remain still in the scanner and ensuring more accurate assessment. Similarly, they have successfully been used to reduce movement inside the scanner in pediatric populations (36). Finally and perhaps more importantly, this approach can determine not only whether any given patient is conscious, but also infer what the contents of that conscious experience might actually be (21), thus revealing important practical and ethical implications for the patient's standard of care and quality of life.

It is hoped that these fMRI-based neuroimaging tests will lead to more accurate prognostication for comatose patients in the near future, and help to better inform end-of-life decisions for vulnerable patients in the critical early stage immediately following catastrophic brain injury.

### 6. ACKNOWLEDGEMENT

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